A review of asymptomatic and sub-clinical Middle East Respiratory Syndrome Coronavirus Infections

Rebecca Grant, Mamunur Rahman Malik, Amgad Elkholy and Maria D Van Kerkhove

Correspondence to Maria D Van Kerkhove, PhD, Department of Infectious Hazards Management, Health Emergencies Program, World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland (e-mail: vankerkhovem@who.int)

Author affiliations: Department of Infectious Hazard Management, WHO Health Emergencies Programme, World Health Organization, Geneva, Switzerland (Maria D Van Kerkhove and Rebecca Grant); Infectious Hazard Management Unit, Department of Health Emergencies, World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt (Mamunur Rahman Malik and Amgad Elkholy); Centre for Global Health, Institut Pasteur, Paris, France (Rebecca Grant).

This research received no external funding.

Conflict of interests: The authors declare no conflict of interest.

Running head: MERS-CoV asymptomatic and sub-clinical infection

ABSTRACT

The epidemiology of Middle East Respiratory syndrome coronavirus (MERS-CoV) since 2012 has been largely characterised by recurrent zoonotic spill-over from dromedary camels followed by limited human-to-human transmission, predominantly in health care settings. The full extent of infection of MERS-CoV is not clear, nor is the extent and/or role of asymptomatic infections in transmission. We conducted a review of molecular and serological investigations through PubMed and EMBASE from September 2012 to 15 November 2018 attempting to measure sub-clinical or asymptomatic MERS-CoV infection within and outside of health care settings. We performed retrospective analysis of laboratory-confirmed MERS-CoV infections reported to the World Health Organization to 27 November 2018 to summarize what is known about asymptomatic infections identified through national surveillance systems. We identified 23 studies reporting evidence of MERS-CoV infection outside health care settings, mainly of camel workers, showing ranges of seroprevalence of 0-67% depending on the study location. We identified 20 studies in health care settings, of health care worker (HCW) and family contacts, of which 11 documented molecular evidence of MERS-CoV infection among asymptomatic contacts. Since 2012, 298 laboratory confirmed cases were reported as asymptomatic to the World Health Organization, 164 of whom were HCW. Viral shedding studies of asymptomatic MERS infections have demonstrated the potential to transmit MERS-CoV to others. Our results highlight the possibility for onward transmission of MERS-CoV from asymptomatic individuals. Screening of HCW contacts of confirmed MERS-CoV patients is currently recommended, but systematic screening of non-HCW contacts outside of health care facilities should be encouraged.

KEYWORDS

MERS-CoV; Seroprevalence; Healthcare Workers; Infection control; Subclinical Infections.

ABBREVIATIONS

HCW, Health care worker; MERS-CoV, Middle East Respiratory syndrome coronavirus;

PCR, Polymerase chain reaction; WHO, World Health Organization.

INTRODUCTION

Since 2012, the epidemiology of cases of Middle East Respiratory syndrome coronavirus (MERS-CoV) infection reported to the World Health Organization (WHO) has been largely characterised by recurrent zoonotic spill-over from the known animal reservoir – dromedary camels – and human-to-human transmission in health care settings (1). Outbreaks in health care settings have on occasion resulted in large outbreaks (2-9). Of the 2260 cases (including 803 deaths) reported to WHO, 83% of cases have been reported in the Kingdom of Saudi Arabia (10).

The clinical presentation of MERS-CoV infection ranges from asymptomatic to severe respiratory illness, with approximately 35.5% resulting in death (1). The role of asymptomatic or subclinical infections in human-to-human transmission of MERS-CoV is not well understood, but there is evidence that laboratory confirmed cases of MERS-CoV infection who are reported as asymptomatic may transmit to other individuals (11).

For many novel infectious pathogens, surveillance initially focuses on individuals with disease presenting to health care facilities, which undoubtedly underestimates the true prevalence of infection, as it will not account for mild or asymptomatic infections not requiring medical care. Detailed outbreak investigations often include laboratory testing of close contacts and of health care workers (HCW), regardless of symptoms, and specialized serological investigations will include individuals thought to be at higher risk of infection, such as those with occupational exposure to animal reservoirs or HCW. Estimates of the true prevalence of infection of high-risk pathogens are important to understand the populations required for vaccine candidates or specific therapeutic treatments as and when they become available. In addition, the role of sub-clinical or asymptomatic infection is critical in

understanding chains of transmission missed by surveillance systems. For MERS-CoV, asymptomatic infection has been reported to WHO, but the possibility of transmission prior to symptom onset is critical for recommending effective infection prevention and control measures and for reducing secondary MERS-CoV transmission.

The role of asymptomatic infections in transmission of other respiratory viruses has been previously investigated. Highly pathogenic avian influenza, H5N1 RNA, for example, has been detected by polymerase chain reaction (PCR) from asymptomatic family contacts of ill patients, suggesting the possibility for onward transmission, even in the absence of symptoms (12-15). For severe acute respiratory syndrome coronavirus (SARS-CoV), transmission risk studies outside health care settings have found limited transmission to close contacts prior to symptom onset or hospitalization, while human-to-human transmission within health care settings was higher, likely due to higher viral load in hospitalised patients and more frequent exposure to the virus among HCW (16-18).

Here, we have reviewed available evidence of the extent of subclinical and asymptomatic infection of MERS-CoV stratified by evaluating studies that have measured infection within and outside of health care settings, and the potential role of onward human-to-human transmission from asymptomatic cases.

METHODS

We conducted a literature search in PubMed and EMBASE databases for observational epidemiological studies of laboratory confirmed MERS-CoV infection using the search terms: ‘MERS-CoV’ or ‘MERS’ AND ‘seroprevalence’ or ‘prevalence’ or ‘serological’ or

'infection' or 'asymptomatic'. Further studies were identified through consultation with the WHO MERS technical network and the bibliography of a related recently published review (19). Publications in English before 15 November 2019 were considered, with no further restrictions on year of publication. We assessed the titles and abstracts of identified studies to determine their eligibility for inclusion in the study. We stratified our analyses to evaluate subclinical and/or asymptomatic infection identified within and outside of health care facilities.

For MERS-CoV infections studied outside health care settings, we included studies reporting evidence of MERS-CoV infection using molecular and/or serological methods in either individuals with occupational exposure to dromedary camels, familial, occupational or social contacts of confirmed MERS patients outside of health care settings, the general population or through national MERS surveillance records, when published. Eligible studies included reporting of the number of individuals tested and the number with molecular or serological evidence of MERS-CoV infection.

To evaluate MERS-CoV infections studied within health care settings, we included studies reporting evidence of MERS-CoV infection using molecular and/or serological methods among HCW and among non HCW contacts (e.g., family contacts) of confirmed MERS cases treated in health care settings.

For each eligible study, we extracted information on the year of publication, the year biological samples were collected, the country of the study, the number of individuals tested, characteristics of the individuals tested, and the total number of confirmed MERS-CoV infections by molecular or serological assay. Asymptomatic MERS-CoV infection was

considered a laboratory confirmed infection with no reported symptoms at the time of sampling.

In addition, we evaluated the symptomatic profile and place of reporting among laboratory confirmed MERS-CoV infections reported to WHO from September 2012 to 27 November 2018. Within WHO databases, cases are classified as primary case: if they were reported as primary cases by the reporting Member State; if they reported direct or indirect contact with dromedary camels or dromedary products; and/or their exposures were under investigation without known contact with a probable or confirmed MERS patient. Cases were classified as secondary cases due to human-to-human transmission if they reported recent direct contact with a known MERS patient and/or were identified as a household, occupational or HCW contact of a known MERS patient.

Descriptive analysis of WHO-case based data used the ggplot2: Elegant Graphics for Data Analysis package in R, version 3.4.2.0 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.).

RESULTS

In total, we identified 43 studies reporting MERS-CoV infections measured by serology and/or molecular testing; 23 focusing on subjects with exposures outside of health care settings (4,7,11, 20-39), and 20 with exposures inside health care facilities (5,7,29,32,40-54). The selection of identified and included studies is shown in Figure 1.

The 23 studies reporting MERS-CoV infections measured by serology and/or molecular testing outside of health care settings are described in Table 1. The majority of studies focused on measuring seroprevalence of MERS-CoV in individuals with occupational exposure to dromedaries in the Middle East and Africa (20-28).

The largest seroprevalence study conducted to date found 0.1% seroprevalence among general population samples collected in 2012-2013, 2% seroprevalence among dromedary camel shepherds and 4% seroprevalence in slaughterhouse workers (37). Further estimates of seroprevalence among occupational high-risk populations ranged from 0-67% with seropositivity being detected in Kingdom of Saudi Arabia, Qatar and Kenya and 0-54% among contacts of confirmed MERS patients in household settings largely in countries of the Middle East. Within these studies, the majority of infections detected by serology appear to be asymptomatic. Within these studies, seropositive camel workers had a high proportion reporting no symptoms (80-100% among seropositive individuals).

Table 2 describes the 20 studies reporting MERS-CoV infections measured by serology and/or molecular testing within health care settings and include studies of HCW and close contacts of confirmed patients. The largest molecular and serological studies among HCW were conducted among 1695 and 1169 HCW in Kingdom of Saudi Arabia (32) and the

Republic of Korea (40) reporting evidence of infection of 1% and 1.5%, respectively. Infection was found to be more frequent among HCW who did not use personal protective equipment when in contact with a MERS patient (40).

Since 2012, 298 of the 2,274 (13.1%) laboratory confirmed cases reported to WHO have been reported as asymptomatic at the time of reporting, 164 of whom were HCW. Table 3 describes the demographic characteristics and clinical presentation of primary and secondary cases of MERS-CoV infection. There were significantly more asymptomatic cases reported among secondary cases (266/1094, 24.3%) compared to primary cases (9/642, 1.4%, p <0.001) Overall, no deaths were reported among asymptomatic infections. Figure 2 shows the epidemic curve of MERS-CoV infections reported to WHO stratified by HCW (A) and non-HCW (B). Of the 414 MERS-CoV infections among HCW which have been reported to WHO, 164 (39.6%) were reported to be asymptomatic.

Evidence of human-to-human transmission from an asymptomatic infection

We found four studies documenting the duration of viral shedding from asymptomatic or mildly symptomatic individuals (55-58). Among asymptomatic PCR positive MERS-CoV infections, positive RT-PCR results were reported from the day of initial testing for as long as 28-42 days (55-58).

We found one study which found molecular and serological evidence of possible secondary transmission from asymptomatic individuals (11). The study was conducted as part of an investigation of 12 household contacts, in which 7 were found to be PCR positive from upper respiratory tract samples and an additional 5 were seropositive using recombinant immunofluorescence or plaque reduction neutralisation test (11). Eleven of these 12

individuals reported no symptoms at the time of sampling and when combined with epidemiological data indicated that they could have been involved in asymptomatic transmission within households.

In health care settings, we found 9 studies which described molecular evidence of MERS-CoV infection among asymptomatic individuals (7,32,42-43,45-46,50-51,53). One study investigated infectivity of an asymptomatic MERS-CoV infected HCW, but found no evidence of secondary transmission to 82 HCW with contact to the MERS-CoV infected HCW (44).

DISCUSSION

In this review, we found 43 studies reporting molecular and/or serological evidence of MERS-CoV infection. Outside of health care settings, the evidence of MERS-CoV infection has largely been focused on individuals with occupational exposure to dromedaries. The results to date are heterogenous and while there have been recent studies attempting to evaluate MERS-CoV genetic diversity (59,60), the differences in seroprevalence results to date likely reflect differences in the selection and characteristics of dromedary herds and humans tested. Based on available evidence of the MERS-CoV epidemiologic and genetic characteristics, there is no current evidence to suggest that there are differences in the virus's ability to infect humans. Evidence supports that subjects with occupational exposure to dromedary camels have higher rates of seroprevalence compared to household contacts of confirmed MERS patients, likely reflecting more intense unprotected exposures to MERS-CoV through dromedary secretions (61). The fact that they have subclinical infection and do not develop disease is likely due to the fact that those with occupational exposure tend to be younger and healthier, without underlying high risk conditions such as hypertension, diabetes and renal failure. Variations in the seroprevalence rates by study are also likely due to

variations in methodologies, including the timing of sample collection, serologic assays used and interpretation of assay results.

While the majority of human infections have been reported to WHO from countries in the Arabian Peninsula, particularly Kingdom of Saudi Arabia, there is increasing evidence of infection in dromedary camels in herds throughout Africa and South Asia (62). Further serological and molecular epidemiology studies at the dromedary-human interface using a standardised approach and consistent methodology, both in the Arabian Peninsula and in Africa and South Asia, are needed to further understand this observed heterogeneity. That is, whether the observed differences in evidence of infection outside health care settings may be attributable to genetic variation of the virus across different geographic regions and/or to factors and behaviours in human populations in these regions which may change the susceptibility to infection. WHO is currently supporting studies evaluating the extent of infection in occupationally exposed persons are underway in a number of countries in the Middle East, Africa and South Asia. The results of such studies can contribute to better understanding the geographic reach of MERS-CoV in dromedaries and humans.

Within health care settings, the detection of asymptomatic PCR positive infection has been reported to WHO from affected member states and also documented in 10 published studies. Although the published studies did not investigate onward transmission, they did capture evidence of RNA shedding, which suggests that human-to-human transmission is possible from individuals with no signs or symptoms of infection. This is supported by evidence documenting duration of viral shedding beyond three weeks in patients with subclinical MERS-CoV infection (55-58).

At the same time, the evidence for acute asymptomatic MERS-CoV infection described in this review does not represent the full extent of sub-clinical infection. Asymptomatic contacts have been shown to clear the virus more quickly than symptomatic patients (58) and antibody titres are likely to be lower, if they seroconvert at all, than infected patients exhibiting symptoms (63). Timely and repeated biological specimen collection is needed to capture viral shedding and antibody kinetics of symptomatic and asymptomatic contacts (11). This can be achieved if all high-risk contacts of confirmed MERS patients are identified during an outbreak and then tested using both molecular and serologic laboratory assays, regardless of whether they exhibit symptoms. In outbreak settings, without the inclusion of testing of all contacts, the identification of chains of transmission may be incomplete.

Indeed, the latest WHO surveillance guidelines recommend that all contacts of a laboratory confirmed MERS cases outside of health care facilities should be placed under active surveillance for 14 days following the last exposure to the confirmed case and that any contacts with symptoms of respiratory illness should be tested for MERS-CoV infection (64). If feasible, we recommend that follow up should include molecular testing, regardless of the development of symptoms. In addition, studies conducted of high-risk workers, which have typically only included serologic testing, should also include molecular testing of upper respiratory samples in an attempt to capture viral carriage.

Despite these limitations in our current knowledge, this review reinforces the evidence that HCW are more likely to be at risk of MERS-CoV infection due to close unprotected contact with MERS patients prior to their diagnosis, particularly when aerosolizing procedures are administered. Because HCW tend to be younger and healthier than patients who develop severe MERS, they have fewer symptoms, if any, and present a silent risk of human-to-human

transmission to others. Among HCW contacts, detailed studies of viral shedding and immune response of asymptomatic PCR positive MERS infections are urgently needed and should be conducted when outbreaks occur and enhanced surveillance is in place by government and hospital officials.

Surveillance and testing for MERS-CoV has improved substantially since the virus was first discovered in 2012. In affected countries, visual respiratory triage systems prior to entrance to emergency departments have been introduced; some emergency departments in affected countries have been restructured for enhanced triage of patients with respiratory symptoms; trainings specific to infection prevention and control of respiratory pathogens have been introduced and reintroduced in high risk areas and hospitals with high turnover of HCW; and audits of hospitals for compliance to specific infection prevention and control measures are regularly performed (6). In addition, the systematic testing of HCW – extending beyond nurses and doctors, but also including reception staff, cleaners, technicians, etc - , regardless of the development of symptoms, as required by the latest infection prevention and control guidelines for HCW by WHO and Kingdom of Saudi Arabia for example, has detected more subclinical and asymptomatic infections, that likely went undetected in past outbreaks. Asymptomatic infections may have played a role in extensive secondary transmission in health care settings before the latest guidelines were introduced, and the impact of such policies may be reflected in the reduced size of the peaks in the global MERS-CoV epidemic curve since 2016. Without this level of contact follow up in community settings, the extent of asymptomatic infections in the community will remain unknown.

Screening of HCW with exposure to MERS-CoV infected patients may be feasible for preventing human-to-human transmission in health care settings, and appears to be effective

in Kingdom of Saudi Arabia and other affected countries in which this infection prevention and control measure has been introduced. Screening of non-HCW contacts in health care settings should also be encouraged. Outside health care settings, the feasibility of screening may be reduced, particularly given the difficulty in detecting asymptomatic infections. Transmission of MERS-CoV outside health care settings should therefore be expected to continue until zoonotic spill-over from dromedaries can be interrupted.

ACKNOWLEDGMENTS

Author affiliations:

Department of Infectious Hazard Management, WHO Health Emergencies Programme, World Health Organization, Geneva, Switzerland (Maria D Van Kerkhove and Rebecca Grant);

Infectious Hazard Management Unit, Department of Health Emergencies, World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt (Mamunur Rahman Malik and Amgad Elkholy);

Centre for Global Health, Institut Pasteur, Paris, France (Rebecca Grant).

Funding: This research received no external funding.

The authors wish to thank public health and animal health workers in affected and at risk member states for their continuous work in identifying MERS-CoV infections in humans and animals.

Conflict of interests: The authors declare no conflict of interest.

REFERENCES

1. World Health Organization. WHO MERS Global Summary and Assessment of Risk: August 2018. Geneva, Switzerland: World Health Organization; 2018 http://www.who.int/csr/disease/coronavirus_infections/risk-assessment-august-2018.pdf (accessed: 18 November 2018)

2. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367(19):1814-20.

3. Hijawi B, Abdallat M, Sayaydeh A, Alqasrawi S, Haddadin A, et al. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. *East Mediterr Health J* 2013; 19:S12-S18.

4. Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *N Engl J Med* 2013; 369(5):407-416.

5. Al-Abdallat MM, Payne DC, Alqasrawi S, Rha B, Tohme RA, Abedi GR, et al. Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. *Clin Infect Dis* 2014; 59 (9):1225-33.

6. Drosten C, Muth D, Corman VM, Hussain R, Al Masri M, HajOmar W, et al. An observational, laboratory-based study of outbreaks of Middle East respiratory syndrome coronavirus in Jeddah and Riyadh, Kingdom of Saudi Arabia, 2014. *Clin Infect Dis* 2015; 60(3):369-77.

7. Al Hosani F, Pringle K, Al Mulla M, Kim L, Pham H, Alami NN, et al. Response to emergence of Middle East respiratory syndrome coronavirus, Abu Dhabi, United Arab Emirates, 2013-2014. *Emerg Infect Dis* 2016; 22(7):1162-8.

8. Ki M. MERS outbreak in Korea: hospital-to-hospital transmission. *Epidemiol Health* 2015; 37: e2015033.

9. Park HY, Lee EJ, Ryu YW, Kim Y, Kim H, Lee H, et al. Epidemiological investigation of MERS-CoV spread in a single hospital in South Korea, May to June 2015. *Euro Surveill* 2015; 20(25):1-6.

10. World Health Organization Regional Office for the Eastern Mediterranean. *MERS situation update, September 2018*. http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-september-2018.html (accessed 29 September 2018)

11. Drosten C, Meyer B, Müller MA, et al. Transmission of MERS-coronavirus in household contacts. *N Engl J Med* 2014; 371(9):828–35.

12. Lu C, Lu J, Chen W, Jiang L, Tan B, et al. Potential infections of H5N1 and H9N2 avian influenza do exist in Guangdong populations of China. *Chin Med J* (Engl) 2008; 121(20):2050-3.

13. Vong S, Ly S, Van Kerkhove MD, Achenbach J, Holl D, et al. Risk Factors Associated with Subclinical Human Infection with Avian Influenza A (H5N1) Virus- Cambodia, 2006. *J Infect Dis*. 2009 Jun 15;199(12):1744-52.

14. Cavailler P, Chu S, Ly S, Garcia J, Ha D, et al. Seroprevalence of anti-H5 antibody in rural Cambodia, 2007. *J Clin Virol*. 2010; 48(2):123-6.

15. World Health Organization. WHO consultation on case management and research on human influenza A/H5. Hanoi, Vietnam, 10–12 May, 2005

16. Isakbaeva ET, Khetsuriani N, Beard RS, Peck A, Erdman D, Monroe SS et al. SARS-associated coronavirus transmission, United States. *Emerg Infect Dis*. 2004; 10(2):225-31.

17. Lau JT, Lau M, Kim JH, Tsui HY, Tsang T, Wong TW. Probable secondary infections in households of SARS patients in Hong Kong. *Emerg Infect Dis*. 2004; 10(2):235-43.

18. Yu WC, Tsang TH, Tong WL, Ng TK, Lim W, Yeung HC et al. Prevalence of subclinical infection by the SARS coronavirus among general practitioners in Hong Kong. *Scand J Infect Dis*. 2004; 36(4):287-90.

19. Hui DS, Azhar EI, Kim YJ, Memish ZA, Oh MD, Zumla A. Middle East respiratory syndrome coronavirus: risk factors and determinants of primary, household, and nosocomial transmission. *Lancet Infect Dis*. 2018; 18(8):e217-e227.

20. Aburizaiza AS, Mattes FM, Azhar EI, Hassan AM, Memish ZA, Muth D et al. Investigation of anti-middle East respiratory syndrome antibodies in blood donors and slaughterhouse workers in Jeddah and Makkah, Saudi Arabia, 2012. *J Infect Dis*. 2014; 209(2):243-6.

21. Chu DK, Poon LL, Gomaa MM, et al. MERS coronaviruses in dromedary camels, Egypt. *Emerg Infect Dis*. 2014; 20(6):1049-53.

22. Hemida MG, Al-Naeem A, Perera RA, Chin AW, Poon LL, Peiris M. Lack of Middle East respiratory syndrome coronavirus transmission from infected camels. *Emerg Infect Dis* 2015; 21(4):699–701.

23. Memish ZA, Alsahly A, Masri MA, Heil GL, Anderson BD, Peiris M et al. Sparse evidence of MERS-CoV infection among animal workers living in Southern Saudi Arabia during 2012. *Influenza Other Respir Viruses*. 2015; 9(2):64-7.

24. Reusken CB, Farag EA, Haagmans BL, Mohran KA, Godeke GJ, Raj S et al. Occupational Exposure to Dromedaries and Risk for MERS-CoV Infection, Qatar, 2013-2014. *Emerg Infect Dis*. 2015; 21(8):1422-5.

25. Liljander A, Meyer B, Jores J, Müller MA, Lattwein E, Njeru I et al. MERS-CoV Antibodies in Humans, Africa, 2013-2014. *Emerg Infect Dis*. 2016; 22(6):1086-9.

26. So RT, Perera RA, Oladipo JO, Chu DK, Kuranga SA, Chan KH et al. Lack of serological evidence of Middle East respiratory syndrome coronavirus infection in virus exposed camel abattoir workers in Nigeria, 2016. *Euro Surveill*. 2018; 23(32).

27. Alshukairi AN, Zheng J, Zhao J, Nehdi A, Baharoon SA, Layqah L et al. High Prevalence of MERS-CoV Infection in Camel Workers in Saudi Arabia. *MBio*. 2018; 9(5).

28. Zohaib A, Saqib M, Athar MA, Chen J, Sial AU, Khan S et al. Countrywide Survey for MERS-Coronavirus Antibodies in Dromedaries and Humans in Pakistan. *Virol Sin*. 2018; 33(5):410-417.

29. The Health Protection Agency (HPA) UK Novel Coronavirus Investigation team. Evidence of person-to-person transmission within a family cluster of novel coronavirus infections, United Kingdom, February 2013. *Euro Surveill*. 2013; 18(11):pii=20427.

30. Omrani AS, Matin MA, Haddad Q, Al-Nakhli D, Memish ZA, Albarrak AM. A family cluster of Middle East Respiratory Syndrome Coronavirus infections related to a likely unrecognized asymptomatic or mild case. *Int J Infect Dis*. 2013;17(9): e668-72.

31. Mailles A, Blanckaert K, Chaud P, van der Werf S, Lina B, Caro V et al. First cases of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human transmission, France, May 2013. *Euro Surveill*. 2013; 18(24). pii: 20502.

32. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, Al-Rabeeah AA, Assiri A, Alhakeem RF. Screening for Middle East respiratory syndrome coronavirus infection in hospital patients and their healthcare worker and family contacts: a prospective descriptive study. *Clin Microbiol Infect* 2014; 20(5): 469–474

33. Arwady MA, Alraddadi B, Basler C, et al. Middle East respiratory syndrome coronavirus transmission in extended family, Saudi Arabia, 2014. *Emerg Infect Dis* 2016; 22(8):1395–402.

34. Plipat T, Buathong R, Wacharapluesadee S, Siriarayapon P, Pittayawonganon C, Sangsajja C et al. Imported case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection from Oman to Thailand, June 2015. *Euro Surveill*. 2017; 22(33). pii: 30598.

35. Al Hosani FI, Kim L, Khudhair A, Pham H, Al Mulla M, Al Bandar Z et al. Serologic follow-up of Middle East Respiratory Syndrome Coronavirus Cases and Contacts - Abu Dhabi, United Arab Emirates. Clin Infect Dis. 2019; 68(3):409-418.

36. Gierer S, Hofmann-Winkler H, Albuali WH, Bertram S, Al-Rubaish AM, Yousef AA et al. Lack of MERS coronavirus neutralizing antibodies in humans, eastern province, Saudi Arabia. *Emerg Infect Dis*. 2013; 19(12):2034-6.

37. Müller MA, Meyer B, Corman VM, et al. Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study. *Lancet Infect Dis* 2015; 15(6):559–64.

38. Munyua P, Corman VM, Bitek A, Osoro E, Meyer B, Müller MA et al. No Serologic Evidence of Middle East Respiratory Syndrome Coronavirus Infection Among Camel Farmers Exposed to Highly Seropositive Camel Herds: A Household Linked Study, Kenya, 2013. *Am J Trop Med Hyg*. 2017; 96(6):1318-1324.

39. Saeed AA, Abedi GR, Alzahrani AG, et al. Surveillance and Testing for Middle East Respiratory Syndrome Coronavirus, Saudi Arabia, April 2015-February 2016. *Emerg Infect Dis*. 2017; 23(4):682-685.

40. Kim CJ, Choi WS, Jung Y, Kiem S, Seol HY, Woo HJ. Surveillance of the Middle East respiratory syndrome (MERS) coronavirus (CoV) infection in healthcare workers after contact with confirmed MERS patients: incidence and risk factors of MERS-CoV seropositivity. *Clin Microbiol Infect*. 2016; 22(10): 880-886.

41. Cho SY, Kang J-M, Ha YE, et al. MERS-CoV outbreak following a single patient exposure in an emergency room in South Korea: an epidemiological outbreak study. *Lancet* 2016; 388(10048):994–1001.

42. Park GE, Ko JH, Peck KR, et al. Control of an outbreak of Middle East respiratory syndrome in a tertiary hospital in Korea. *Ann Intern Med* 2016; 165(2):87–93.

43. Hastings DL, Tokars JI, Abdel Aziz IZ, Alkhaldi KZ, Bensadek AT, Alraddadi BM et al. Outbreak of Middle East Respiratory Syndrome at Tertiary Care Hospital, Jeddah, Saudi Arabia, 2014. *Emerg Infect Dis*. 2016; 22(5):794-801.

44. Moon SY, Son JS. Infectivity of an asymptomatic patient with Middle East respiratory syndrome coronavirus infection. *Clin Infect Dis* 2017; 64(10):1457–58.

45. Alfaraj SH, Al-Tawfiq JA, Memish ZA. Middle East respiratory syndrome coronavirus intermittent positive cases: Implications for infection control. *Am J Infect Control*. 2019; 47(3):290-293.

46. Amer H, Alqahtani AS, Alaklobi F, Altayeb J, Memish ZA. Healthcare worker exposure to Middle East respiratory syndrome coronavirus (MERS-CoV): Revision of screening strategies urgently needed. *Int J Infect Dis*. 2018; 71:113-116.

47. Amer H, Alqahtani AS, Alzoman H, Aljerian N, Memish ZA. Unusual presentation of Middle East respiratory syndrome coronavirus leading to a large outbreak in Riyadh during 2017. *Am J Infect Control*. 2018; 46(9):1022-1025.

48. Alshukairi AN, Khalid I, Ahmed WA, Dada AM, Bayumi DT, Malic LS et al. Antibody Response and Disease Severity in Healthcare Worker MERS Survivors. *Emerg Infect Dis*. 2016; 22(6).

49. Assiri A, Abedi GR, Bin Saeed AA, Abdalla MA, al-Masry M, Choudhry AJ et al. Multifacility Outbreak of Middle East Respiratory Syndrome in Taif, Saudi Arabia. *Emerg Infect Dis*. 2016; 22(1):32-40.

50. Balkhy HH, Alenazi TH, Alshamrani MM, Baffoe-Bonnie H, Arabi Y, Hijazi R et al. Description of a Hospital Outbreak of Middle East Respiratory Syndrome in a Large Tertiary Care Hospital in Saudi Arabia. *Infect Control Hosp Epidemiol*. 2016; 37(10):1147-55.

51. Alenazi TH, Al Arbash H, El-Saed A, Alshamrani MM, Baffoe-Bonnie H, Arabi YM et al. Identified Transmission Dynamics of Middle East Respiratory Syndrome Coronavirus Infection During an Outbreak: Implications of an Overcrowded Emergency Department. *Clin Infect Dis*. 2017; 65(4):675-679.

52. Oboho IK, Tomczyk SM, Al-Asmari AM, Banjar AA, Al-Mugti H, Aloraini MS et al. 2014 MERS-CoV outbreak in Jeddah--a link to health care facilities. *N Engl J Med*. 2015; 372(9):846-54.

53. Zhao J, Alshukairi AN, Baharoon SA, Ahmed WA, Bokhari AA, Nehdi AM et al. Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. *Sci Immunol*. 2017; 2(14). pii: eaan5393.

54. Payne DC, Biggs HM, Al-Abdallat MM, Alqasrawi S, Lu X, Abedi GR et al. Multihospital Outbreak of a Middle East Respiratory Syndrome Coronavirus Deletion Variant, Jordan: A Molecular, Serologic, and Epidemiologic Investigation. *Open Forum Infect Dis*. 2018; 5(5):ofy095.

55. Al-Gethamy M, Corman VM, Hussain R, Al-Tawfiq JA, Drosten C, Memish ZA. A Case of Long-term Excretion and Subclinical Infection With Middle East Respiratory Syndrome Coronavirus in a Healthcare Worker. *Clin Infect Dis* 2015; 60(6):973–4

56. Al-Abdely HM, Midgley CM, Alkhamis AM, et al. Infectious MERS-CoV Isolated From a Mildly Ill Patient, Saudi Arabia. *Open Forum Infect Dis*. 2018;5(6):ofy111.

57. Corman VM, Albarrak AM, Omrani AS, Albarrak MM, Farah ME, Almasri M et al. Viral Shedding and Antibody Response in 37 Patients With Middle East Respiratory Syndrome Coronavirus Infection. *Clin Infect Dis*. 2016; 62(4):477-483.

58. Memish ZA, Assiri AM, Al-Tawfiq JA. Middle East respiratory syndrome coronavirus (MERS-CoV) viral shedding in the respiratory tract: an observational analysis with infection control implications. *Int J Infect Dis*. 2014; 29:307-8

59. Chu DKW, Hui KPY, Perera RAPM, et al. MERS coronaviruses from camels in Africa exhibit region-dependent genetic diversity. *Proc Natl Acad Sci USA.* 2018; 115(12):3144-3149.

60. Kiambi S, Corman VM, Sitawa R, et al. Detection of distinct MERS-Coronavirus strains in dromedary camels from Kenya, 2017. *Emerg Microbes Infect* 2018; 7(1):195.

61. Sikkema RS, Farag EABA, Himatt S et al. Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Infection in Camel Workers in Qatar During 2013-2014: A Case-Control Study. *J Infect Dis*. 2017; 215(11):1702-1705.

62. FAO-OIE-WHO MERS Technical Working Group. MERS: Progress on the global response, remaining challenges and the way forward. *Antiviral Res*. 2018; 159:35-44.

63. Park WB, Perera RA, Choe PG, et al. Kinetics of Serologic Responses to MERS Coronavirus Infection in Humans, South Korea. *Emerg Infect Dis*. 2015; 21(12):2186-9.

64. World Health Organization. Surveillance for human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) Interim guidance June 2018. Geneva, Switzerland: World Health Organization; 2018. http://www.who.int/csr/disease/coronavirus_infections/surveillance-human-infection-mers/en/ (accessed: 18 November 2018)

Figure 1: Flow diagram of selection of articles for the review of symptomatic and sub-clinical Middle East Respiratory Syndrome coronavirus Infections

Additional records identified through consultation with the WHO MERS technical network and the bibliography of a related recently published review (19).

Abbreviations: MERS-CoV, Middle East Respiratory Syndrome Coronavirus

Figure 2. Epidemic curve of laboratory-confirmed Middle East Respiratory Syndrome coronavirus infections among Health care workers (A) and non-Health care workers (B) and outcome reported to the World Health Organization from 2012 to 27 November 2018

Table 1: Evidence of MERS-CoV infection outside health care settings, 2012-2018

First Author, Year (Reference No.)	Study dates (in years)	Location of study	Number of subjects	Description of subjects	Laboratory results	Evidence of asymptomatic MERS-CoV infection among PCR/serologically positive subjects
Occupational exposure to dromedary camels						
Aburizaiza, 2014 (20)	2012	KSA	226	Slaughterhouse workers	0 (0%) had specific antibodies against MERS-CoV (immunofluorescence assay and neutralisation)	
Chu, 2014 (21)	2013	Egypt	179	Camel abattoir workers	0 (0%) had serological evidence of MERS-CoV infection	
Hemida, 2015 (22)	2013-2014	KSA	191	Occupational exposure to dromedary camels	0 (0%) had specific antibodies against MERS-CoV (ppNT)	
Memish, 2015 (23)	2012	KSA	75	Direct contact with domestic animals including camels	0 (0%) had specific antibodies against MERS-CoV (ppNT)	
Reusken, 2015 (24)	2013-2014	Qatar	294	Daily occupational contact with dromedary camels	10 (3.4%) had specific neutralising antibodies against MERS-CoV (ELISA and $PRNT_{90}$)	10 (100%) reported no severe health problems
Liljander, 2016 (25)	2013-2014	Kenya	1222	Livestock handlers in Kenya	2 (0.2%) had confirmed serological evidence of MERS-CoV infection (recombinant ELISA, $PRNT_{50}$ and $PRNT_{90}$)	2 (100%) reported no recent clinical symptoms, indication mild or subclinical infection
So, 2018 (26)	2016	Nigeria	261	Abattoir workers with exposure to dromedary camels	0 (0%) had specific neutralising antibodies against MERS-CoV (ELISA and ppNT)	
Alshukairi, 2018 (27)	2018	KSA	30	Camel herders, truck drivers and handlers	20 (67%) seropositive for MERS-CoV infection (ELISA, $PRNT_{50}$ and MERS-CoV specific T cell response)	6 (20%) reported fever/cold in the previous 4 months

Zohaib, 2018 (28)	2016-2017	Pakistan	840	Camel herders	0 (0%) had serological evidence of MERS-CoV infection (ELISA, $PRNT_{50}$)	
Contacts of confirmed MERS patients outside health care settings						
Health Protection Agency, 2013 (29)	2013	United Kingdom	33	Close contacts of a confirmed case	2 (6%) had molecular evidence of MERS-CoV infection (RT-PCR)	0 (0%) were asymptomatic
Assiri, 2013 (4)	2013	KSA	217	Household contacts of confirmed cases	5 (2%) had confirmed MERS-CoV infection (RT-PCR and viral load)	Not reported
Omrani, 2013 (30)	2013	KSA	10	Household contacts of confirmed cases	0 (0%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Mailles, 2013 (31)	2013	France	162	Contacts of a confirmed case	1 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	0 (0%) were asymptomatic
Memish, 2014 (32)	2012-2014	KSA	462	Family contacts of confirmed cases	10 (2%) had molecular evidence of MERS-CoV infection (RT-PCR)	Not reported
Drosten, 2014 (11)	2013	KSA	280	Household contacts of confirmed cases	12 (4%) had laboratory evidence of secondary MERS transmission (RT-PCR, ELISA, recombinant immunofluorescence assay, $PRNT_{50}$, $PRNT_{90}$)	11 (92%) were asymptomatic
Arwady, 2016 (33)	2014	KSA	79	Relatives of MERS-CoV infected patients	11 (14%) had molecular evidence of MERS-CoV infection (RT-PCR); 8 (10%) additional contacts had serological evidence of MERS-CoV infection (ELISA)	2 (11%) reported mild symptoms and 3 (16%) were asymptomatic
Plipat, 2017 (34)	2015	Thailand	48	High risk contacts of a confirmed case	0 (0%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Al Hosani, 2018 (35)	2013-2018	United Arab Emirates	124	Case patients and household contacts of MERS-CoV patients	13 (54%) cases had MERS-CoV antibodies; 0 (0%) household contacts had serological evidence of MERS-CoV infection (ELISA and microneutralisation)	3 of 13 case patients (23%) were asymptomatic
General population						
Gierer,	2010-2012	KSA	268	Children hospitalised for	0 (0%) had specific neutralising	

2013 (36)				lower respiratory tract infection and male blood donors	antibodies against MERS-CoV (lentiviral vector system)	
Müller, 2015 (37)	2012-2013	KSA	10009	Healthy individuals across all 13 provinces of KSA	15 (0.1%) had anti-MERS-CoV antibodies (recombinant ELISA, recombinant immunofluorescence assay, $PRNT_{50}$ and $PRNT_{90}$)	Not reported
Munyua, 2017 (38)	2013	Kenya	760	Households exposed to seropositive camels	0 (0%) had specific neutralising antibodies against MERS-CoV (ELISA and $PRNT_{50}$)	
Retrospective review of national surveillance records						
Al Hosani, 2016 (7)	2013-2014	United Arab Emirates	1586	Suspected MERS case patients from surveillance records	65 (4%) had molecular evidence of MERS-CoV infection (RT-PCR)	23 (35%) were asymptomatic
Saeed, 2017 (39)	2015-2016	KSA	57363	Suspected MERS case patients	384 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	19 (5%) were asymptomatic

Abbreviations: KSA, Kingdom of Saudi Arabia; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; ELISA, Enzyme-linked immunoassay; ppNT, pseudoparticle neutralisation test; $PRNT_{50}$, 50% plaque reduction neutralisation test; $PRNT_{90}$, 90% plaque reduction neutralisation test; RT-PCR, Reverse transcriptase polymerase chain reaction.

Table 2: Evidence of MERS-CoV infection in health care settings, 2012-2018

First Author, Year (Reference No.)	Study dates (in years)	Location of study	Number of individuals tested	Description of subjects	Laboratory results	Evidence of asymptomatic MERS-CoV infection among PCR/serologically positive subjects
HCW contacts of confirmed MERS-CoV patients						
Health Protection Agency, 2013 (29)	2013	United Kingdom	59	HCW	0 transmission (RT-PCR)	
Memish, 2014 (32)	2012-2013	KSA	1695	HCW	19 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	2 (11%) were asymptomatic ; 5 (26%) had mild infection
Kim, 2016 (40)	2015	ROK	1169	HCW	17 (1%) had evidence of MERS-CoV infection, higher among HCW who did not use PPE (ELISA and Indirect immunofluorescence test)	
Cho, 2016 (41)	2015	ROK	218	HCW	8 (4%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Park, 2016 (42)	2015	ROK	519	HCW	3 (1%) had molecular evidence of MERS-CoV infection (RT-PCR)	3 (100%) were asymptomatic
Hastings, 2016 (43)	2014	KSA	16	HCW	14 (88%) had molecular evidence of MERS-CoV infection (RT-PCR)	13 (81%) were asymptomatic
Moon, 2017 (44)	2015	ROK	82	HCW	0 transmission from asymptomatic HCW (RT-PCR and ELISA)	
Alfaraj, 2018 (45)	2015	KSA	153	HCW	7 (5%) had molecular evidence of MERS-CoV infection (RT-PCR)	5 (71%) were asymptomatic
Amer, 2018	2017	KSA	879	HCW	17 (2%) had molecular evidence	17 (100%) were asymptomatic or

(46)					of MERS-CoV infection (RT-PCR)	had mild disease
Amer, 2018 (47)	2017	KSA	107	HCW	9 (8%) positive for MERS-CoV (RT-PCR)	
Asymptomatic infection among infected HCW						
Alshukairi, 2016 (48)	2014-2016	KSA	NR	HCW	18 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA)	6 (33%) were asymptomatic
Assiri, 2016 (49)	2014-2015	KSA	NR	HCW	7 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT)	4 (57%) were asymptomatic
Balkhy, 2016 (50)	2015	KSA	NR	HCW	43 had molecular evidence of MERS-CoV infection (RT-PCR)	25 (58%) were asymptomatic
Al Hosani, 2016 (7)	2013-2014	United Arab Emirates	NR	HCW	31 had molecular evidence of MERS-CoV infection (RT-PCR)	12 (39%) were asymptomatic
Alenazi, 2017 (51)	2015	KSA	NR	HCW	43 had molecular evidence of MERS-CoV infection (RT-PCR)	18 (42%) were asymptomatic
2018[a]	2012-2018	Global	NR	HCW	389 had laboratory confirmed MERS-CoV infection	94 (24%) were asymptomatic
MERS-CoV infection in health care settings among non-health care workers						
Al-Abdallat, 2014 (5)	2012-2013	Jordan	124	Contacts identified during MERS outbreak	9 (7%) had serological evidence of MERS-CoV infection (ELISA, IFA, MT)	0 (0%) were asymptomatic
Cho, 2016 (41)	2015	ROK	675	Patients in hospital, contacts of MERS-CoV infected cases	33 (5%) had molecular evidence of MERS-CoV infection (RT-PCR)	
Extent of asymptomatic infection among laboratory confirmed MERS cases						
Oboho, 2015 (52)	2014	KSA	NR	Confirmed MERS-CoV infection	255 had molecular evidence of MERS-CoV infection (RT-PCR)	64 (25%) patients were asymptomatic - although 26 patients interviewed reported at least 1 symptom consistent with respiratory illness
Assiri, 2016 (49)	2014-2015	KSA	NR	Confirmed MERS-CoV infection	38 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT)	2 (5%) were asymptomatic

Alenazi, 2017 (51)	2015	KSA	NR	Patient-contacts in hospital	61 had molecular evidence of MERS-CoV infection (RT-PCR)	3 (5%) were asymptomatic
Zhao, 2017 (53)	2015	KSA	NR	MERS survivors	18 had molecular and serological evidence of MERS-CoV infection (RT-PCR, ELISA, IFA, MT, $PRNT_{50}$ and MERS-CoV specific T cell response)	3 (17%) were asymptomatic; patients with higher $PRNT_{50}$ and T cell responses had longer intensive care unit stays
Payne, 2018 (54)	2015-2016	Jordan	NR	Patient-contacts in hospital	16 had laboratory confirmed MERS-CoV infection (RT-PCR, ELISA, MT)	3 (19%) were asymptomatic

Abbreviations: HCW, Health care worker; KSA, Kingdom of Saudi Arabia; ROK, Republic of Korea; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; NR, Not reported; ELISA, Enzyme-linked immunoassay; IFA, immunofluorescence assay; MT, microneutralization assay; PRNT, Plaque reduction neutralisation test; RT-PCR, Reverse transcriptase polymerase chain reaction

[a] Unpublished data, source: World Health Organization 2018

Table 3: Description of characteristics of MERS-CoV infection reported to WHO from September 2012 to 27 November 2018

	Reported source of Infection					
MERS case characteristics	Outside health care settings (*n* = 764)		Within in health care setting (*n* = 826)		Not known at the time of reporting to WHO (*n* = 681)	
	No.	%	No.	%	No.	%
Case classification						
Primary case[a]	561	73.4	2	0.2	79	11.6
Secondary case[b]	193	25.3	816	98.8	85	12.5
Unknown at the time of reporting	10	1.3	8	1.0	517	75.9
Primary MERS-CoV infection[a]						
Age[c]	55.9 (45.0-69.0)		47.0 (39.0-55.0)		57.8 (46.0-72.0)	
Sex						
Male	459	81.8	2	100	72	91.1
Female	102	18.2	0	0	5	6.3
Comorbidities						
Any	316	56.3	1	50	17	21.5
None	62	11.1	0	0	3	3.8
Not reported	183	32.6	1	50	59	74.7
Clinical presentation						
Asymptomatic	7	1.2	0	0	2	2.5
Symptomatic	521	92.9	2	100	65	82.3
Not reported	33	5.9)	0	0	12	15.2
Outcome						
Survived	167	29.8	1	50	14	17.7
Died	277	49.4	0	0	32	40.5
Not reported	117	20.8	1	50	33	41.8
Secondary MERS-CoV infection[b]						
Age[c]	40.7 (27.0-54.0)		49.3 (34.0-62.0)		42.7 (28.0-54.0)	
Sex						
Male	124	64.2	451	55.3	51	60
Female	69	35.8	365	44.7	34	40
Comorbidities						
Any	47	24.4	281	34.4	13	15.3
None	43	22.3	104	12.7	10	11.8
Not reported	103	53.4	431	52.8	62	72.9
Clinical presentation						
Asymptomatic	74	38.3	180	22.1	12	14.1
Symptomatic	103	53.4	482	59.1	51	60
Not reported	16	8.3	154	18.9	22	25.9
Outcome						
Survived	127	65.8	337	41.3	28	32.9
Died	27	14.0	248	30.4	20	23.5
Not reported	39	20.2	231	28.3	37	43.5

Abbreviations: MERS-CoV, Middle East Respiratory Syndrome Coronavirus; WHO: World Health Organization; IQR: interquartile range

[a] Primary infection: reported direct or indirect contact with dromedary camels, no contact with a probable or confirmed MERS-CoV infected human case, no prior health care facility contact (*n* =642)

[b] Secondary infection: direct epidemiological link to a human MERS infection (n =1094)

[c] Values are expressed as mean (interquartile range)